A View on the 2003 Proposed Cancer Guidelines for Early Life Exposure (April 18, 2003)

Dennis J. Paustenbach (Menlo Park, CA)

On February 28, 2003 the United States EPA issued the "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens" [hereafter called Guidance]. This has also been nicknames the “Cancer Guidelines for Children”. Unlike many other guidelines, the EPA states in the Preface that “…this Supplemental Guidance will have no binding effect on EPA or any regulated entity”. However, the EPA noted that it reserves the right to use the "approaches in Supplemental Guidance in developing a future risk assessment...[if] the approaches from the Supplemental Guidance that were employed are suitable and appropriate." As a practical matter, it is quite likely that the final version of this guidance will have significant impact on future decisions by the EPA and the courts.

Like so many regulatory policies, guidance or criteria this is a “good news/bad news" story. The good news is that the EPA apparently believes that the United States has the financial resources to more thoroughly investigate whether low level exposure to carcinogens at an early age (e.g., neonate or young child) poses a larger cancer risk than for adults exposed to the same dose. Most risk assessors and/or toxicologists who have studied carcinogens for the past two decades have suspected that the fetus was more susceptible than the adult to a later cancer hazard from some genotoxic chemicals; but only if the dose was substantial. By substantial, it was meant at the doses used in cancer bioassays or, perhaps, at doses to which some people might be exposed in the workplace. The toxicology community has assumed, based on various lines of reasoning and basic scientific principles, that the doses associated with current regulations contain a sufficient margin of safety to protect children.

The bad news is that there is a dearth of published information upon which to offer quantitative, or even qualitative, guidance. In short, there have not been any published studies conducted which were specifically designed to answer the question which the EPA and the scientific community would like to address. The Guidance does a good job of piecing together the very limited information from various studies to suggest that the young child probably is more susceptible to mutagens during periods of rapid organ development. However, there is very little acknowledgment by the EPA in this draft guidance that the doses in the studies they rely upon were significantly, often 1000 fold, above any likely environmental dose.

It should be noted that EPA is not intending this Guidance to prevent childhood cancers but rather as a mechanism for reducing adult cancers due to early life-time exposure. Also, the guidance only addresses exposure after birth and does not consider the possible risks associated with prenatal exposure through the mother.

Background

The EPA correctly notes in its Supplemental Guidance that standard animal cancer bioassays generally begin dosing after the animals are 6-8 weeks old, when many organs and systems are relatively mature, though substantial growth in body size continues thereafter. In the few review articles that compare the results of perinatal carcinogenesis testing to the standard cancer bioassay, the authors usually note that (1) the same tumor sites are usually observed following either perinatal or adult exposure and (2) perinatal exposure in conjunction with adult exposure usually increases the incidence of tumors or reduces the latency period before tumors are observed. As noted previously, the extrapolation of this information from relatively high dose animal studies to infer that children, for example, are more susceptible to chemicals found in the air, water, food or soil is not easily justified given the available information.

In the Introduction, the Agency correctly notes that there are a number of possible reasons why young children could be more susceptible to the adverse effects of chemicals but the Guidance

document tends to talk more about evidence for the developmental hazard than evidence that they are more susceptible to carcinogens. They list a few characteristics of early development, which if perturbed, might increase the cancer hazard including:

- More frequent cell division during development can result in enhanced fixation of mutations due to the reduced time available for repair of DNA lesions. Also, clonal expansion of mutant cells gives a larger population of mutants
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes
- Some components of the immune system are not fully functional during development
- Hormonal systems operate at different levels during different life stages
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life

It should be noted, however, that the above list definitely describes why, following exposure to chemicals at some dose, the fetus or young child is vulnerable to developmental effects but the list is not nearly so compelling as evidence for an increased cancer hazard. Moreover, the Guidance specifically states that the safety factors apply to children after birth, not fetuses, and the data on which these factors are based do not include prenatal exposure. To the EPA's credit, it recognizes that the available data only suggest that the genotoxic carcinogens might be of concern and they acknowledge that a lot more information is needed.

Mode Of Action

As in the primary document, the EPA's Draft Final Guidelines for Carcinogen Risk Assessment (www.epa.gov/ncea/raf/cancer2003.htm), a significant amount of discussion is directed at the importance of the mode of action through which a chemical produces its carcinogenic effect. For those scientists who have studied the mechanism of action of the various classes of chemical carcinogens or specific chemicals, this section deserves special attention, as it is in many ways the foundation upon which Guidance is based.

Without going into a detailed discussion of whether or not there is sufficient evidence to indicate that certain modes of action present a greater carcinogenic hazard for the neonate or young child compared with the adult, there are a few parts of the EPA discussion which probably would benefit from comments of substance from members of the scientific community. In particular, there seems to be some degree of reliance on the assumption that cancer risks are proportional to exposure duration. Although the assumption as applied in the Guidance is acknowledged to be a bit weak, it is nonetheless later used as a basis for some of the quantitative recommendations. The EPA is aware that it had difficulty coming up with a good estimate of the daily dose when trying to apply information from animals studies not intended to assess risk to the young animals. This is because the young animals eat and drink larger quantities per body weight when they are young. This, regrettably, complicates the quantitative interpretation of most of the published studies.

Not surprisingly, perhaps the best information for determining whether the neonate or child is at greater risk of developing cancer (per unit of dose) than adults is contained within the radiation literature. Again, EPA acknowledges that there are very substantial differences between the toxicokinetics and toxicodynamics of mutagenic chemicals and ionizing radiation however, due to a paucity of good studies on chemicals, they tend to rely on information from the A-bomb survivors for inferring an increased cancer risk to children. Because of the reliance on the radiation literature, it is clear throughout the document that EPA would like to focus on the possible increased susceptibility of children to chemicals which are clearly genotoxic. Even though this is a prudent approach, it would have been useful for EPA to have spent more time

discussing why exposure to relatively high doses of ionizing radiation is different from exposure to low doses of even fairly potent genotoxic chemical carcinogens.

The Database

Twenty three animal studies on sixteen chemicals are used to derive some level of qualitative and quantitative understanding of the increased susceptibility of the young child. The primary data sets relied upon by the EPA derive from seven multiple dose studies of the five mutagenic compounds, benzo[a]pyrene, benzidine, diethylnitrosamine, safrole, and vinyl chloride and six multiple dose studies of six non-mutagenic carcinogens. The EPA readily acknowledged that these studies were not designed to answer the questions being asked. Many more data sets investigating exposure of young animals to mutagens and carcinogens are available. However, in an attempt to use the data to answer the question at hand-does early life exposure increase carcinogenic risk-the EPA chose to only use studies from the same laboratories, using the same species and strain of animal, the same route of exposure and similar doses.

The EPA attempts to adjust or normalize the doses from the studies of the five mutagens and six non-mutagens so that it can determine if a consistent message surfaces from this data set. That is, because the studies do not have an accurate estimation of dose for the young animals, the agency uses time as a surrogate for dose. Since these studies were not intended for the purpose to which EPA would like them to apply, it is quite possible that no matter how much the data are scrutinized, no light will be shed on the central issue of the Supplemental Guidance, e.g. are children genuinely more susceptible to low doses of chemical carcinogens.

The rest of the discussion about the database is clear and relatively concise. In fact, this Guidance document is as readable and understandable as any of the dozens of documents EPA has produced over the past 30 years. The thought process was relatively easy to follow. However, the handling of data from the various studies that are presented in the tables was not easy to follow. Specifically, it was not always clear why certain data were presented from the studies and not others. In addition, the use of acute dosing studies, without appropriate complementary long-term studies, to try to understand the cancer hazard seemed to involve a lot of wishful thinking on the part of the Agency. Also, there was not sufficient discussion of the importance of separating those chemicals requiring activation (metabolism) to form the reactive chemical species versus those that are direct acting carcinogens. This is important because, when compared to the adult, one of the genuine differences between the fetus, the newborn, and the developing child, is that certain metabolic enzymes are not fully functional. Thus, if metabolic activation of a chemical is required, the fetus or young child would be less susceptible to the carcinogenic hazard compared to later in life.

One could take issue with the mathematical model used by EPA (i.e., the ratio of early exposure tumor incidence/ratio of adult exposure tumor incidence =risk adjustment factor) since it may mask two significant problems with the methodology. First, EPA is not sure of the dose to the young animals in the various studies. Second, one might expect that earlier exposure would shift the latency curve to the left, thus resulting in an apparent increase in tumors. The Agency would do well to reexamine this method.

The database and results section closes with a discussion of "carcinogen with modes of action other than mutagenicity." It seems that the Agency simply had to concede that not enough is known about the non-genotoxic chemicals at this time to conclude that they do or do not pose an increased cancer hazard to children at any dose. This was courageous and, given what is known, a valid position.

Implementation Guidance For Assessing Cancer Risks From Early-Life Exposure

This section is only about 5 pages in length but the Agency makes a number of recommendations that are surely going to stimulate discussion within the scientific community.

In an attempt to give the Supplemental Guidance some substance, the Agency offers some quantitative recommendations about estimating the cancer risk to children. One must assume that these recommendations were thought to be reasonable given the data that was presented in the 23 animals studies and what was learned from the human experience with ionizing radiation. These recommendations, in fact, are useful for generating thoughtful discussion and for generating research hypotheses but are probably lacking sufficient foundation to warrant being the basis of the EPA's future risk assessments of scenarios involving newborns or young children.

The key recommendations within this section are almost certainly those listed in item 2a on page 34. "When the data indicate a mutagenic mode of action, the available science indicates that higher cancer risks typically result from a given exposure occurring early in life when compared with the same amount of exposure during adulthood. Consequently, in the absence of early-life studies on a specific agent under consideration, U.S. EPA generally should:

- Use linear extrapolation to lower doses. This choice is based on mode-of-action data indicating that mutagens can give risk to cancers with an apparently low-dose-linear response.

- Adjust risk estimates that pertain to childhood exposure. This choice is proposed because risk estimates based on a lifetime-average daily dose do not consider the potential for higher cancer risks form early life exposure. The following adjustments represent a practical approach that reflects the results of the preceding analysis, which found that cancer risks generally were higher from early-life exposure than from similar exposure durations in life:

    - For exposures before 2 years of age, a 10-fold adjustment.

    - For exposures between 2-15 years of age, a 3 fold-adjustment

    - For exposures after 15 years of age, no adjustment

  These adjustments reflect the potential for early-life exposure to make a greater contribution to cancers appearing later in life; any differences in early life also should be accounted for."

Other general recommendations are offered and although one can support many of them and take issue with others, they do not have the potential impact on health risk assessment of the abovementioned recommendations.

One View of the Guidelines

It was only a matter of time before the environmental revolution, which began nearly 40 years ago, would have the luxury of having a serious debate about whether the standards or guidelines that were initially established to protect both adults and children were truly adequate to protect the unborn (or the newborn). Many of the genuinely significant, and obvious, public health hazards associated with the presence of industrial chemicals in our environment have been identified and regulated. To a large extent, the concentrations to which the vast majority of

Americans are now exposed are quite small. It has been inferred that, therefore, the possible risks to the typical America must also be quite small.

However, as the Agency points out, an argument can be made that it is logical to infer that children may well be at some greater risk of harm to some agents simply because they inhale and ingest larger quantities per body weight than adults, and because cell turnover is great during the periods of development; thus increasing the risk of mutations if there is exposure to a genotoxic agent. Indeed, this is true if the doses which may result even from compliance with current environmental regulations do not have an appreciable margin of safety built into them. The scientific community does not have solid information to indicate that the majority of current regulations do not have an adequate margin of safety to protect children. On the other hand, it is probably not possible to demonstrate complete safety one way or the other using either animal or epidemiology studies.

This brings up a point worth mentioning. Ever since the passage of the Food Quality Protection Act (FQPA), many people have suggested that current exposure limits of all types (i.e., air, food, water, soil) have not originally intended to protect children. This is not the case. Going back to the work of Dr. Arnold Lehman, children were considered by the FDA in the 1950s when tolerances were established using the safety factor approach. Children were also considered in the first Carcinogenic Risk Assessment Guidelines promulgated by the EPA in 1976. One is hard pressed to find many examples where this approach has not been adequate in protecting our children. However, as noted previously, it is difficult to show that there is a large margin of safety inherent in these criteria.

This particular Supplemental Guideline is, in all likelihood, representative of the next generation of guidelines to be issued in the United States and Western Europe. The goal is to keep the pressure on society to be vigilant about how it uses chemicals and releases them into the environment. To apply this pressure is, de facto, the duty of the EPA. Twenty years ago, issuance of these kinds of guidance documents or assessments of particular agents was termed "science forcing". That is, the EPA or other agencies announced that it was going to issue strict regulations in light of the possible hazards to workers or society unless the regulated community would conduct the scientific research convincing them that the risk was, in fact, negligible. Regrettably, this approach has not been used as frequently over the past decade.

Some might claim, as the EPA has indicated, that because this Guidance is not binding, then it will have only modest impact on how risk assessments are conducted in the coming years. This is probably naive. History is quite clear that even draft EPA guidelines take on a life of their own; both here and in other countries. Further, EPA headquarters has only limited control over what the Regional offices of EPA do with its draft or final guidelines. For those who might not believe this, one need only look at the decision by EPA Region V to rely upon the EPA's Draft Dioxin Reassessment as part of its justification for not accepting a rather important risk assessment submitted by Dow Chemical for its Midland site (even though reliance on draft documents is discouraged by EPA headquarters).

Because of the increasing expectations of citizens for cleaner air, water, food, soil and sediments the Agency has a mandate to be absolutely certain that current guidelines are amply protective. This is the rub; the science on the increased susceptibility of children compared to adults is simply not available, and it may not be obtainable, to answer these questions. For this reason, adoption of the Precautionary Principle has significant appeal to some citizens and many non-governmental organizations. Many may believe that it is regrettable, but for multiple reasons, legal and otherwise, the Agency is not yet able to implement the Precautionary Principle. However, the Agency is able to conduct analyses like those presented in the so-called "Children's Cancer Guidelines" and use them to suggest that quantitative changes in how the country conducts risk assessments are needed. Whether this Guidance meets the expectation of the new Data Quality Act is unclear.

When faced with the very sparse data upon which the recommendations are based, to the extent that the Agency is in fact embracing the Precautionary Principle, it should say so. Perhaps, the Agency would be better off to simply state that "in light of the concern about this possible hazard, we recommend that the following approach be implemented beginning one to five years from the date of issuance unless certain data gaps are filled." Accordingly, it would be useful if the Agency, based on their efforts to develop these guidelines, identified the areas of research that could potentially satisfy their concerns and negate the need for promulgating the recommendations contained in these guidelines. Perhaps the regulated community and academia would then rise to the occasion and help inform future decisions about the possible risk to children.

Applying the "science forcing" approach is likely a more useful approach to achieving what the citizens expect of the EPA without going through the process of trying to make the available data support a position for which the data are inadequate. Virtually all companies and scientists find it difficult to "not support" reducing the concentrations of chemicals in our environment and it is especially difficult not to support efforts that might ultimately be of some benefit to our children. If the Agency believes that some action is needed, it would be more appropriate for them to simply say they were embracing the Precautionary Principle as the justification for their recommendations rather than try to rely on the available data.

This is not to say that I embrace or reject the Precautionary Principle. For one thing, there are many different proposed approaches for implementing the principle. The advantage of the approach is that it is simple. Some variations of the Principle, including those which require corporations to arbitrarily reduce emissions of specific contaminants by 50% every 5 years, have certain benefits over traditional approaches to dealing with chemicals. This approach has proven to be effective, for example, in the Scandinavian countries where it was applied to the emissions of dioxins. However, one of the biggest shortcomings is that the approach is expensive and it is a poor tool for prioritizing the hazards posed by the 2,000 or more chemicals used frequently in industry. In short, the hazard is that the nation might spend a great deal of money controlling trivial hazards at the expense of not dealing with those that are significant.

The Agency has probably done the best job that it can with what is known about the possible increased susceptibility of children but it is not sufficient to warrant the quantitative recommendations offered by EPA. If adopted, the costs of dealing with the more strict clean-up and emissions limits could be quite substantial. For example, already some prognosticators have indicated that these Guidelines to support requests to "reopen" Records of Decisions at Superfund sites across the nation. These people allege that "new evidence has been presented in these guidelines" and that one can infer that these sites were not cleaned to standards which will protect children.

There are, in my view, many other more pressing environmental issues worthy of our attention which don't require the leaps of faith that are needed to embrace these proposed guidelines. Eliminating certain known health hazards for children, improving the public education about lifestyle choices and promulgating rules for some chemicals in our environment which have yet to be regulated would almost certainly be more likely to improve the well being of children than applying these broad recommendations to future risk assessments. Nonetheless, as a society we have rightfully decided to focus on the potential hazard to children posed by chemicals in our environment and I would not be opposed to supporting many of the recommendations in this Supplemental Guidance but it would be inappropriate for society to think that the "science was telling us to do it".

Note: The author was asked by the BNA to write this commentary. He received no compensation for the research efforts or time invested in its development.